

How Pharmacogenomics Will Revolutionize Oncology Clinical Trials

Richard Pazdur, MD
Director, Oncology Drug Products
United States Food and Drug Administration

Today's Topics

- **Pharmacogenomics and Safety**—defining new doses in PG-defined subpopulations to improve safety: 6-Mercaptopurine, Irinotecan
- **Pharmacogenomics and Efficacy**—defining new populations to enhance efficacy: Epidermal Growth Factor Receptor (EGFR) tyrosine kinase Inhibitors—Iressa (gefitinib) and Tarceva (erlotinib)

Basis for NDA Approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies
- Ability to generate product labeling that
 - Defines an appropriate patient population for treatment with the drug
 - Provides adequate information to enable safe and effective use of the drug

21 CFR 201.57

- If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with the disease, the labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug.

Aspects of Oncology Drug Development

- Life-threatening nature of diseases—patient access, use of placebos
- Drugs used in combination
- Risk/benefit ratio—different perspective on toxicities; trained specialists using drugs
- Product label and off-label uses
- Lack of predictive efficacy models—high risk drug development
- Use of drugs by oncologists, clinical trials community

Dilemma of Dose

- Maximum tolerated dose vs biologically directed dose
- Early dose-efficacy relationships based on surrogate endpoint (response rate)
- Surrogate may not capture true clinical benefit of the drug (survival, TTP)
- Difficulty of examining dose post-approval
- Lack of PD relationship to clinical benefit or surrogates

6-Mercaptopurine

- Approved by FDA for the treatment of acute leukemia in 1953
- Has been used as a component of anti-leukemic therapy in pediatric oncology for 50 years
- Extensive clinical experience in management of dose, toxicity

6MP and Childhood Leukemia

- ALL is a life-threatening disease
- 6-MP can cause life-threatening toxicities
- Dose titration (dose, duration, and intensity) is a major determinant of efficacy and toxicity (myelosuppression)
- 6-MP is metabolized to active thiopurine nucleotides by thiopurine methyltransferase (TPMT)

TPMT Genetic Polymorphism

- Documented link between TPMT polymorphism and toxicity
- Genotypes with reduced (10% of population) and absent (0.3%) are at increased risk of myelosuppression and possible secondary cancers.
- Pharmacogenetic tests available and feasible to use for identifying patients

Pharmacogenetic Tests

- TPMT genotype predicts no or very low enzyme activity
 - Results in excess accumulation of RBC of active thioguanine nucleotides
 - TPMT phenotype measures rbc enzyme activity

Pediatric Subcommittee

- July 15, 2003 to seek advice on additional information to be included in the product label with regard to TPMT metabolic activity and testing and the potential toxicity to pediatric patients with ALL

Advisory Committee

- Language should be added to convey that only persons who have the homozygous condition are at high *and consistent* risk of developing toxicity
- Preliminary data indicate that more than half of the heterozygous persons can tolerate standard doses
- Patients with normal TPMT can have severe toxicity; hence, a normal test does not preclude severe toxicity

Advisory Committee

- Statements that laboratory tests are available to determine TPMT status of pediatric patients should be included in product label
- No further recommendations on use or interpretation of tests be made
- No specific dose adjustments or starting dose should be included

Advisory Committee--4

- No recommendation for testing status of TPMT activity on all children (or during first week) of 6-MP initiation should be made.
- Recommendation for testing if severe myelosuppression occurs

Concerns of Test

- Extensive experience with drug and clinical dose modification based on toxicity
- High cure rate with current therapy with generally acceptable toxicity profile (for oncology drug)
- Fear that mandated testing may lead to under-dosing and reduced cure rates
- Fear that mandated testing may result in delay in treatment initiation
- Legal consequences of testing or failing to test

New Product Label (under Pharmacokinetics)

- Includes information on incidence of TPMT
- TPMT genotyping and phenotyping (rbc TPMT activity) can identify patients who are homozygous deficient or heterozygous patients with low or intermediate TPMT activity
- Substantial dose reductions are generally required for homozygous patients
- Accumulation of excessive cellular concentrations of active nucleotides by homozygous patients

New Product Label (under WARNINGS)

- Homozygous patients (2 non-functional alleles)--unusually sensitive to myelosuppressive effects
- Lab tests available for genotyping and phenotyping
- Substantial dose reductions for homozygous patients; heterozygous patients may have increased toxicity, but this is variable and some may tolerate normal doses
- If a patient has severe toxicity, TPMT test should be considered

Product Label—Testing (under PRECAUTIONS)

- Genotypic and phenotypic testing of TPMT are available
- Genotypic testing can determine the allelic pattern. Currently, 3 alleles—TMPT *2, TMPT *3A, TMPT *3C—account for about 95% with reduced activity
- Individuals homozygous for these alleles are TPMT deficient and heterozygous patients may have variable TPMT activity (low or intermediate)

Product Label—Dosage and Administration

- Dosage in TPMT-deficient Patients—Patients with little or no TPMT activity are at increased risk for severe toxicity from conventional doses of mercaptopurine. Dosing should be reduced and carefully monitored in homozygous-deficient patients who have little or no TPMT activity. Genotypic and phenotypic testing of TPMT status are available.

Conclusions—6MP

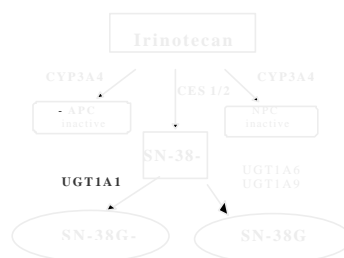
- No regulatory barrier for inclusion of pharmacogenetic data into label
- A regulatory mandate exists to provide information on safety and effectiveness in subgroups and identification of tests needed for selection or monitoring
- Scientific rationale must precede regulatory action
- Acceptance by medical investigators and subsequent implementation into medical practice

Pharmacogenetics of Irinotecan: Scientific and Clinical Evidence

Indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum.

Indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

Metabolic Pathways



UGT1A1 Pharmacogenetics

- UGT1A1 has more than 30 variant alleles.
- UGT 1A1*28 is a variant allele
- Variation in the TA repeats in the promoter region
 - Normal allele: 6 TA repeats (6/6)
 - Variant allele: 7 TA repeats (7/7)
 - UGT 1A1*28 is associated with reduced gene expression and reduced glucuronidation in human liver microsomes.

UGT1A1 Pharmacogenetics

UGT1A1 gene shows trimodal variation in the North American population

Genotype	Percent Population
6/6	~ 50
6/7	~ 40
7/7	~ 10

6 = 6 TA repeats; 7 = 7 TA repeats

Prospective Study

- 66 patients received irinotecan every 3 weeks.
- Homozygous TA7 genotype patients had a relative risk of 9.3 (95% CI, 2.4 to 36.4) for grade 4 neutropenia.
- 50% (3 out of 6) of the homozygous TA7 patients had grade 4 neutropenia compared to 12.5% heterozygous TA6/7 patients (3 out of 24).
- No patients with the normal TA6 genotype (0 out of 29) had any grade 4 neutropenia.
- SN-38 exposure directly correlated with the UGT1A1 genotype.

Product Label Revisions—Clinical Pharmacology

- SN-38 is subsequently conjugated predominately by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite
- UGT1A1 activity is reduced in individuals with genetic polymorphisms that led to reduced enzyme activity such as UGT1A1*28 polymorphism
- Approximately 10% of the North American Population is homozygous for UGT1A1*28 allele.
- In a prospective study....patients who were homozygous for UGT1A1*28 had a higher exposure to SN-38 than patients with wild-type UGT1A1 allele

WARNINGS

- Individuals homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following CAMPTOSAR
- A reduced initial dose should be considered for homozygous patients
- Heterozygous patients (carriers for one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at an increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

DOSAGE AND ADMINISTRATION

A reduction in the starting dose by one level may be considered in patients ≥ 65 years, prior radiotherapy, performance status 2, increased bilirubin levels.

*A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele...The appropriate dose reduction in this patient population is not known.*

UGT1A1 Testing—Clinical Considerations

- Prospective dose reductions in PG-directed “at risk” patients
- Consideration of therapeutic alternatives in PG-directed “at risk” patients

EGFR

- What is the EGFR role in cancer?
 - ErbB1 first sequenced in a four-member family of structurally related type or subclass 1 receptors known as tyrosine kinases.
 - Critical for mediating the proliferation and differentiation of normal cell growth
 - Widely expressed in epithelial, mesenchymal, and neuronal tissues
 - Aberrant activation of the kinase activity of these receptors appears to play a primary role in solid tumor development and/or progression
 - Breast, brain, lung, cervical, bladder, gastrointestinal, renal, and head and neck squamous cell carcinomas, have demonstrated an over expression of EGFR relative to normal tissue, which is associated with a poor clinical prognosis



FDA News

FOR IMMEDIATE RELEASE
P03-36
May 5, 2003

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Type of Drug for Lung Cancer

The Food and Drug Administration (FDA) today announced the approval of Iressa (gefitinib) tablets as a single agent treatment for patients with advanced non-small cell lung cancer (NSCLC), the most common form of lung cancer in the U.S. Iressa is being approved as a treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy, two drugs that are currently the standard of care in this disease.

Iressa was reviewed and approved under FDA's accelerated approval program, which is intended to allow patients suffering from serious or life-threatening diseases earlier access to promising new drugs. As required by the accelerated approval regulations, Iressa's developer will perform additional studies to verify the drug's clinical benefit.

"FDA believes it is crucial for cancer patients to have many safe and effective treatment options available to them in their battle against this disease," said FDA Commissioner Mark B. McClellan, M.D., Ph.D. "With the approval of Iressa, thousands of patients with lung cancer will now have access to an additional treatment after others haven't worked to stop the progression of their disease."

The mechanism by which Iressa exerts its clinical benefit is not fully understood. However, Iressa was developed to block growth-stimulating signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Iressa blocks several of these tyrosine kinases, including the one associated with Epidermal Growth Factor Receptor (EGFR).

FDA based the approval on the results of a study of 216 patients with NSCLC, including 142 patients with refractory disease, i.e., tumors resistant or unresponsive to two prior treatments. The response rate (defined as at least 50% tumor shrinkage lasting at least one month) was about 10%. There were more dramatic responses in some patients and the median duration of response was 7 months. On September 24, 2002, the Oncologic Drug Advisory Committee (ODAC) recommended that in first-line treatment of NSCLC, where there are no viable treatment options, a 10% response rate was reasonably likely to predict clinical benefit and recommended that Iressa be approved.

Results from two large, controlled, randomized trials in initial treatment of NSCLC showed no benefit from adding Iressa to standard, platinum-based chemotherapy. Therefore, Iressa is not indicated for use in this setting.

Subgroups

- Higher responses rates noted in Japanese trials
- Response rates appeared to be highly variable in subgroups of the treated population
- US registration trials: 10.6% response rate
 - 5% in males, 17.5% in females
 - 4.6% in smokers, 29.4% in non-smokers
 - 12.4% in adenocarcinomas, 6.7% other NSCLC

News

Contact the NCI Press Office



Posted: 04/29/2004

Page Options
Print This Page
Email This Document

Find News Releases

Search For:

Between these dates:

Jan 1998 Jul

Jan 2005 Jul

Go

Search Marks

Volume 4, Issue 4

Natural Products for Cancer

Media Resources

Historical documents

Presence of Gene Mutation Tightly Linked to Drug Effectiveness in Lung Cancer

Mutation of a gene involved in non-small cell lung cancer (NSCLC) increases the likelihood that the drug gefitinib (Iressa™) will show a beneficial response, researchers at the Dana-Farber Cancer Institute, the National Cancer Institute (NCI)—part of the National Institutes of Health—and two other institutions announced today in the online version of *Science*. Previously, gefitinib had been shown to cause tumor regression in certain patients, but researchers had not been able to predict which patients would be responsive to the drug. With this discovery, doctors will be able to select those lung cancer patients who could most benefit from gefitinib and may identify additional patients with other types of cancer who may respond to similar treatments.

The mutation discovered was in the epidermal growth factor receptor (EGFR), a gene that codes for an enzyme in the tyrosine kinase family of proteins. Tyrosine kinases are a class of enzymes involved in cellular signaling that have been shown to undergo mutations in various cancers. Inhibition of this type of enzyme has recently been a focus for scientists, but gefitinib had not been as effective as some had expected based on earlier clinical trials conducted in Japan.

The gene mutations identified in this study cause the kinase to be overactive. The sensitivity to gefitinib in both patients entered into a clinical trial and to tumor cells grown in a lab was shown to be highly correlated with the presence of tumors that contained these EGFR mutations. While this type of drug sensitivity was shown earlier for the drug imatinib (Gleevec™), which is most effective against certain leukemias and gastrointestinal stromal tumors that possess specific genetic mutations, this is the first demonstration of a targeted therapy in a common adult malignancy.

"One of the more striking results we found in this study was the difference in response between Japanese and American patients, which raises the question of genetic variation in different ethnic, cultural, and geographic groups to this particular drug," said Bruce E. Johnson, M.D., Dana-Farber Cancer Institute, who led the Lung Cancer Biology Section at NCI before leaving for Dana-Farber.



This is a revised version of an FDA statement originally issued December 17, 2004. Information on Alimta was added to the fourth paragraph.

FDA Statement

FOR IMMEDIATE RELEASE
Statement
December 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Statement on Iressa

The FDA today released the following statement regarding the failure of a clinical trial of Iressa (gefitinib) to show an overall survival advantage in treating patients with lung cancer:

The Food and Drug Administration (FDA) learned yesterday from AstraZeneca that a large clinical trial comparing Iressa (gefitinib) with placebo in patients with non-small cell lung cancer who had failed other courses of cancer therapy showed no survival benefit from taking Iressa.

Patients currently taking Iressa should consult with their physicians as soon as possible; patients should not change their therapy without first consulting with their physicians.

Alternative therapies are available. FDA has approved Taxotere (docetaxel) and Tarceva (erlotinib), both of which have been shown in studies to improve survival in patients with non-small cell lung cancer whose cancer has progressed while on previous therapies. Alimta (gemtuzumab) has received an accelerated approval based on the surrogate endpoint for this use but has not yet demonstrated any survival benefit.

FDA approved Iressa on May 2, 2003, under the Agency's accelerated approval (Subpart H) program, for the treatment of patients with non-small cell lung cancer who had failed two or more courses of chemotherapy. The accelerated approval provisions in FDA's regulations allow the agency to approve a drug for marketing based on an effect on a surrogate endpoint—such as a sign of a disease or the results of a laboratory test—that is considered reasonably likely to predict clinical benefit (improved symptoms or survival). Iressa was approved because the data from clinical trials showed that it caused significant shrinkage in tumors in about 10% of patients, and this was thought likely to increase patients' overall survival time.

Clinical Trial Results

Summaries of Newsworthy Clinical Trial Results
[Back to Main](#)



Posted: 05/05/2004

Page Options

Print This Page

Email This Document

Search by Cancer Type

Breast Cancer

Lung Cancer

Prostate Cancer

Stomach Cancer

Go

Search Results

Quick Links

Director's Corner

Updates from the Director

Colloquium

Cancer-related items

Feature Commentaries

Research and Training

NCI Publications

Office/Institute News

NCI Calendar

Erlotinib (Tarceva®) Extends Survival in Advanced Lung Cancer

Key Words

Lung cancer, non-small cell lung cancer, erlotinib (Tarceva®)
(Definitions of many terms related to cancer can be found in the [Cancer.gov Dictionary](#).)

Summary

Erlotinib (Tarceva®) prolonged survival in patients with advanced non-small cell lung cancer who had progressed after standard chemotherapy.

Source

American Society of Clinical Oncology (ASCO) annual meeting, New Orleans, June 5, 2004.

Background

Up to now, patients with advanced non-small cell lung cancer who have relapsed after standard therapy have had few treatment options. Erlotinib is a [targeted drug](#) taken by mouth that works by interfering with cell signals controlled by a protein called the epidermal growth factor receptor (EGFR). This protein, also called HER1, is found on the surface of many tumor cells and affects tumor growth. Erlotinib is not yet approved by the U.S. Food and Drug Administration.

Related Pages

Search for Clinical Trials

NCI PDQ® database of cancer clinical trials

Lung Cancer, Home Page

NCI gateway for information about lung cancer

Statistics from ASCO 2004

A collection of links to material summarizing some of the important clinical trial results announced at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO).



FDA News

FOR IMMEDIATE RELEASE
P04-105
November 19, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Drug for the Most Common Type of Lung Cancer Drug Shows Survival Benefit

The Food and Drug Administration (FDA) announced the approval of Tarceva (erlotinib) tablets as a single agent treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), the most common form of lung cancer in the U.S. Tarceva is being approved as a treatment for patients whose cancer has continued to progress despite other treatments, including at least one prior chemotherapy regimen.

Tarceva is a drug that inhibits an enzyme, tyrosine kinase, associated with a Human Epidermal Growth Factor Receptor. The drug has shown improved survival in patients with locally advanced or metastatic NSCLC. Tarceva received "Fast Track" status from FDA during its development.

"FDA believes it is crucial for cancer patients to have many safe and effective treatment options available to them in their battle against this disease," said Dr. Lester M. Crawford, Acting FDA Commissioner. "With the approval of Tarceva thousands of patients with lung cancer will not only have access to another treatment option, but one that extends life."

Safety and efficacy were demonstrated in one randomized trial in 731 patients comparing Tarceva to placebo. The primary endpoint in this trial was survival. The median overall survival was 6.7 months in the Tarceva group compared with 4.7 months in the placebo group.

The mechanism of action by which Tarceva exerts its clinical benefit is not fully understood. However, Tarceva was developed to block growth-stimulating signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Tarceva blocks the tyrosine kinase associated with Epidermal Growth Factor Receptor (EGFR).

In about one third of the patients tumor cells were examined to see whether they had high or low levels of EGFR. Among the approximately 55% who had high EGFR the effect on survival was much greater than it was in people whose EGFR levels were low. The relationship will be explored further in the future.

Tarceva vs Placebo

- 488 on Tarceva, 242 on placebo
- Survival: Tarceva median 6.7 months, placebo median 4.7 months, $p < 0.001$, HR 0.73
- Improvement in progression-free survival ($p < 0.001$)
- Improvement in response rate 8.9 vs 0.9% ($p < 0.001$) and response duration

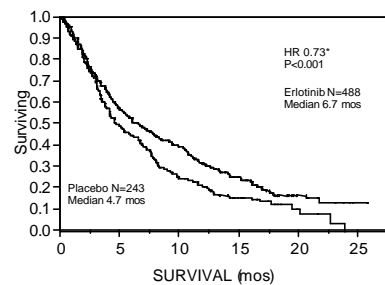
Exploratory Univariate Analyses

- "The effect of TARCEVA on survival was similar across most subsets. An apparently larger effect, however, was observed in two subsets: patients with EGFR positive tumors (HR = 0.65) and patients who never smoked (HR = 0.42)."
- "Tarceva prolonged survival in the EGFR positive subgroup and subgroup whose EGFR status was unmeasured, but did not have an effect on survival in the EGFR negative subgroup"
- Confidence intervals for the three EGFR groups wide and overlap so that survival benefit in the EGFR negative subgroup cannot be excluded.

Exploratory Analyses

- "For the subgroup of patients who never smoked, EGFR status also appeared to be predictive of Tarceva survival benefit. Patients who never smoked and were EGFR positive had a large Tarceva survival benefit (N=30, HR=0.27, 95% CI= 0.11-0.67) There were too few EGFR negative patients who never smoked to reach a conclusion."
- Impact of EGFR status on tumor response rate (11.6% in EGFR positive and 3.2% on EGFR negative) and progression-free survival also noted

Figure 1. Survival By Treatment N=731



*HR is from the Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum and best response to prior chemotherapy. P-value is from two-sided Log Rank test stratified by ECOG performance status, number of prior regimens, prior platinum and best response to prior chemotherapy.

Figure 3. Survival EGFR Positive By Treatment N=127

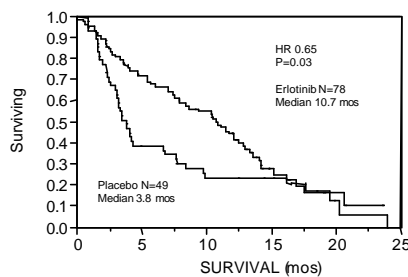


Figure 4. Survival EGFR Negative By Treatment N=111

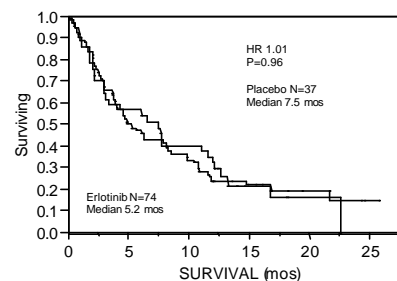


Figure 8. Survival Never Smoked EGFR Positive By Treatment

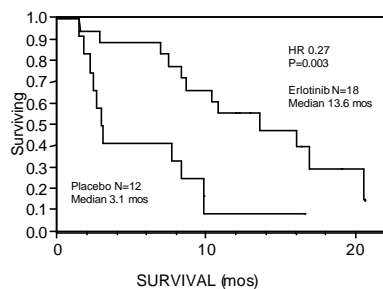
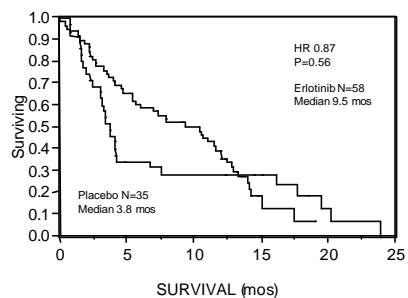


Figure 10. Survival Smokers EGFR Positive by Treatment



Subgroup Analyses

- Drugs designed to target the EGF receptor
- Patients not selected for EGFR measurement
- Hazard ratios for Tarceva survival effect were very similar in overall, measured EGFR, and unmeasured populations
- Consistent results in secondary endpoints
- Need for prospective study—tissue collection
- Implications for “class effect”

Parting Comments

- Conventional cytotoxic drug development—achieves little benefit in a large patient population
- Targeted drug development by PG—may define large benefit in smaller population
- Commercial Concerns—limit populations for efficacy claim; competitive disadvantage if test required
- May exclude patients who would benefit due to unrecognized/additional mechanisms

Parting Comments

- “Theoretical” targeted drug versus a “true” targeted drug—must *clinically* define a population more likely to receive benefit
- Re-defining “conventional” definitions of diseases: a new paradigm for drug development—New business models, New partnerships within industry, government, academics, regulatory flexibility